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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 3518.1015-000

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on November 27, 2006

Signature: Amy Comeau

Typed or printed name: Amy T. Comeau

Application Number	Filed
10/630,227	July 30, 2003

First Named Inventor: Thomas M. DiMauro

Art Unit	Examiner
1647	Shulamith H. Shafer

Applicant requests review of the ~~final~~ rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

Please see the attached Pre-Appeal Brief Conference Remarks.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 42,122
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Deirdre E. Sanders
Signature

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November 27, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Application No.: 10/630,227 Group: 1647

Filed: July 30, 2003 Examiner: Shafer, Shulamith H

Confirmation No.: 8291

For: TRANS-CAPSULAR ADMINISTRATION OF HIGH SPECIFICITY CYTOKINE INHIBITORS INTO ORTHOPEDIC JOINTS

CERTIFICATE OF MAILING OR TRANSMISSION

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11-27-2006 Amy Comeau
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Amy Comeau
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PRE-APPEAL CONFERENCE REMARKS

Mail Stop AF
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Sir:

In response to the Office Action mailed from the U.S. Patent and Trademark Office on June 27, 2006, Applicants respectfully request a pre-appeal brief conference. A Notice of Appeal and petition for extension of time are being filed concurrently with this request. In the Office Action, the Examiner twice rejected pending Claims 1, 2, 34, 36-43, 45-51, 53-58, 60-61 and 63-65, and newly rejected Claim 62 and new elected claims 89-92. The pending claims are provided in the Amendment dated April 4, 2006 ("Amendment").

I. Claims 1, 2, 34, 36, 37, 39-43, 45, 47, 49, 51, 53, 54, 56-58 and 60-65 are not obvious

The primary reference cited in the obviousness rejections is Lehman *et al.*, *The Journal of Pediatrics, 140*:125-127 (2002)) ("Lehman *et al.*"). Applicants' claims are directed to treatment of an inflamed orthopedic joint by *trans-capsular administration into the joint space* of a formulation comprising *an inhibitor of TNF-α synthesis.* Claim 1 is the only pending independent claim.

In order for claims to be deemed obvious, there must have been motivation to combine the references to practice this invention with a reasonable expectation of success. Hindsight speculation is not permissible. Lehman *et al.* teach that two children with systemic onset juvenile rheumatoid arthritis were systemically treated with etanercept (ENBREL®) and thalidomide. Although treatment with etanercept was unsuccessful, treatment with thalidomide resulted in improvements. Lehman *et al.* teaches that thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity, and notes that it may increase TNF-α production under some circumstances (see page 126, column 3). In fact, Lehman *et al.* cites Reference No. 14, which teaches that thalidomide does not reduce TNF-α levels. (Exhibit A, Gori *et al.*, *J. Infect. Dis. 182*:639-640 (2000), filed with Amendment) In fact, Gori *et al.* reported a progressive increase in TNF-α production following thalidomide treatment. Thus, although thalidomide can inhibit on TNF-α synthesis, it was known to have stimulatory effects as well. Further, Gori *et al.* states that, in light of these results, they suggest "extreme caution" in undertaking studies that support *any* clinical use of thalidomide.

Therefore, Lehman *et al.* teach systemic administration, not administration via trans-capsular injection into a joint space. Further, Lehman *et al.* do not teach or suggest treatment with an inhibitor of TNF-α synthesis. In fact, Lehman *et al.* teach administration of a substance known to have at least some stimulatory effects on TNF-α activity (thalidomide), for which those in the art warned of a need for "extreme caution" for *any* clinical use of thalidomide.

Thus, Lehman *et al.* do not provide one of skill in the art with a reasonable expectation of successfully treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis. None of the references cited in the obviousness rejections, when combined with Lehman *et al.* provide the necessary motivation to combine to practice the claimed invention. (See also Amendment, pages 18-25).

A. Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56: These claims have been rejected as being unpatentable over Lehman *et al.* in view of Dunn (EP 1 153 606)("Dunn"). Dunn teaches treating an

inflamed joint by injecting growth hormone and buffer solution into the joint space. (*See* Dunn, col. 7, par. 0027). Dunn further discloses that ENBREL® can be injected with a growth hormone and buffer solution into the joint space. (See Dunn abstract and col. 8, par. 0030; col. 9, par. 0031). However, ENBREL® does not inhibit TNF-α synthesis. According to the Examiner, the reference also teaches injection of anti-cytokines "which would by definition include an inhibitor of TNF-α synthesis". However, a vast number of anti-cytokines are, in fact, not inhibitors of TNF-α synthesis, and there is no reason to believe that teachings of administration of the general category of anti-cytokines would necessarily, by definition, include teaching an inhibitor of TNF-α synthesis. As repeatedly noted by the Federal Circuit, mere possibility or probability does not prove inherency. Dunn does not describe administration of an inhibitor of TNF-α synthesis.

B. Claims 36, 39-43, 45, 58, 60-65: These claims have been rejected as being unpatentable over Lehman *et al.* in view of Pike *et al.* (US Publication No. 20030134792). These claims are dependent on Claim 1, and contain additional elements regarding administration, including delivery systems and devices. Pike *et al.* discloses the treatment of articular cartilage disorders by administering IGF-1 (a growth factor) by, for example, intra-articular injection. According to the Examiner, the reference also teaches that the composition may comprise anti-inflammatory agents "which would include an inhibitor of TNF-α synthesis". However, a vast number of anti-inflammatory agents are, in fact, not inhibitors of TNF-α synthesis, and teachings of administration of a general category of anti-inflammatory agents do not inherently include an inhibitor of TNF-α synthesis. Pike *et al.* does not teach or suggest administering an inhibitor of TNF-α synthesis.

C. Claims 1, 50, 53, 55 and 57: Claim 50 has been rejected as being unpatentable over Lehman *et al.* and Dunn as applied to Claims 1 and 49 and Molloy *et al., Sports Med.*, 33: 381-394 (2003). According to the Examiner, Molloy *et al.* teach that PDGF plays a role in tendon healing. Claim 53, Claim 57 and Claim 1 have been rejected as being unpatentable over Lehman *et al.* in view of Smith *et al.* (U.S. Publication No. 20020169162). Smith *et al.* teaches surgically implanting intraarticularly, *i.e.*, within the synovial joint, a sustained release device which is capable of releasing drugs or compounds over an extended period of time in a controlled fashion, as opposed to repeated injections (See pars 0012, 0046 and 0047). Thus, Smith *et al.* teaches away from administration by injection, as this term was understood by those of ordinary skill in the art. (See pars. 006-008). Claim 55 has been rejected as being unpatentable over Lehman *et al.* and Dunn as applied to Claim 1 and Cardone *et al., American Family Physician,* 67: 2147-2152 (2003). Neither Molloy *et al.* nor Smith *et al.*, nor Cardone *et al.*,

teach treatment of an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis.

One of ordinary skill in the art would not have been motivated to combine the teachings of Lehman *et al.* and any of the above references, alone or in combination, to treat an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis with any reasonable expectation of success. Thus, the claims are not obvious.

D. Claim 1: has been newly rejected as being unpatentable over Dunn in view of Braun *et al., Expert Opin. Biol. Ther.* 3: 141-168 (2003). Dunn does not describe administration of an inhibitor of TNF-α synthesis. Braun teaches use of infliximab, a chimeric anti-TNF antibody, to treat rheumatoid arthritis by single intravenous infusions. It does not teach or suggest trans-capsular administration into a joint space, nor does it teach any potential value of any local administration. One of skill in the art would not have been motivated to combine Braun *et al.* with a reference teaching an alternate mode of administration with an expectation of success. Thus, Claim 1 is not obvious.

II. Claims 38 and 48 are Definite

According to the Examiner, since an inhibitor of TNF-α synthesis covers compounds of different molecular weights, sizes and structures, "the recitation of specific dosages are meaningless". Applicants respectfully disagree. Methods of measuring compounds in formulations was well known and highly routine in the art at the time of the invention. Further, the terms are discussed in the specification at page 23, lines 6-21. Particularly to one of ordinary skill in the art, the terms "100 mg/ml" and "0.5 mg" would be clear in claims reciting an inhibitor of TNF-α synthesis "present in the formulation in an amount of at least 100 mg/ml" and "present in the formulation in a maximum amount of 0.5 mg." Thus, the claims are definite.

III. Claims 38, 48 and 49 are Enabled

It would not take undue experimentation to perform the invention claimed in Claims 38 and 48. The level of skill in the relevant art is high. Techniques to measure weight and volume were well-known in the art at the time of the invention. As noted by the Federal Circuit, enablement is not precluded by necessity for some experimentation such as routine screening. One of skill in the art of inflamed knee joint treatment could easily determine how to measure any inhibitor of TNF-α synthesis in a formulation in an amount of at least 100 mg/ml or in a formulation in a maximum amount of 0.5 mg

without undue experimentation. Applicants are willing to cancel rejected Claim 46 to reduce issues and further prosecution.

The Examiner states that Claim 49 (wherein the formulation further comprises a growth factor present in an amount effective to repair joint tissue) is not enabled because the specification fails to teach the skilled artisan how to use the factors recited without undue experimentation to determine whether a given protein would be useful in the claimed methods and what the dosage would be. The specification discusses the factors in detail, (e.g., page 32, line 11-page 33, line 2). The level of skill in the relevant art is high, and therapeutic administration of growth factors was well-known at the time of the invention. A skilled practitioner could easily determine whether an inflamed knee joint is being treated, and how to determine appropriate dosage of known factors for such treatment.

IV. Claim 49 Complies with the Written Description Requirement

As noted by the Examiner, the specification lists a myriad of growth factors that may be used in the invention. (*See, e.g.,* page 32, line 11-page 33, line 2) As further noted by the Examiner, the skilled artisan would be aware of a number of different compounds which would be classified under the heading "growth factors". Clearly, the claimed subject matter is described in the specification in a manner which does demonstrate that the applicants had possession of the specific subject matter claimed.

CONCLUSION

In view of the above remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

Respectfully submitted,

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